REMARKS/ARGUMENTS

I. Status of the claims

With entry of this Amendment, claim 95 is amended. Claims 95-107 are currently pending. Claims 99, 102, 104 and 105 were withdrawn by the Examiner due to non-elected species. Claims 95-98, 100, 101, 103, 106 and 107 are being examined.

II. Support for the amendments

Amendments to the claims made in this amendment find support throughout the specification as filed, including, for example, paragraph 162 of the specification. The amendments introduce no new matter into the specification.

III. Non-Compliant Amendment

The Examiner issued a Notice of Non-Compliant Amendment on September 24, 2007, indicating that withdrawn claims were not provided with the proper status identifier. The Listing of Claims in the present amendment contains the corrected status identifiers. Applicants have included a petition for a one-month extension of time for response, from October 24, 2007 through November 24, 2007, in connection with this response to the Notice of Non-Compliant Amendment.

IV. Rejection under 35 U.S.C. § 112

The Examiner rejected claims 95-98, 100, 101, 103, 106 and 107 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that the specification does not explicitly define the phrase 'non-naturally-occurring amino acids sequences', and maintains that it is not clear what sequences the term encompasses and what sequences are excluded by the term. The Examiner states that the term 'non-naturally-occurring amino acids sequences' should be given its broadest *reasonable* interpretation (emphasis added), stating that a so-called "wild-type" sequence known in the art may or may not fall within the scope of non-naturally-occurring sequences, and

implying that the phrase can refer to constructs having sequences found in nature, but that are produced by man (presumably in a laboratory).

The Applicants respectfully traverse this rejection. The Applicants submit that the interpretation offered by the Examiner is not, in fact, reasonable, when viewed in light of the specification, the prosecution history and the usage of the term in the art.

Every portion of the specification providing context for and examples of what is meant by 'non-naturally-occurring' as applied to monomer domains relates to methods that can be used to change one sequence (e.g., a naturally-occurring sequence) to an altered sequence (e.g., a non-naturally-occurring sequence). See, e.g., the first part of paragraph 162 in the specification:

> [162] The non-natural monomer domains or altered monomer domains can be produced by a number of methods. Any method of mutagenesis, such as site-directed mutagenesis and random mutagenesis (e.g., chemical mutagenesis) can be used to produce variants. In some embodiments, error-prone PCR is employed to create variants. Additional methods include aligning a plurality of naturally occurring monomer domains by aligning conserved amino acids in the plurality of naturally occurring monomer domains; and, designing the non-naturally occurring monomer domain by maintaining the conserved amino acids and inserting, deleting or altering amino acids around the conserved amino acids to generate the non-naturally occurring monomer domain. In one embodiment, the conserved amino acids comprise cysteines. In another embodiment, the inserting step uses random amino acids, or optionally, the inserting step uses portions of the naturally occurring monomer domains.

Paragraph 162 and others like it list methods and techniques that may be used to introduce changes into the sequence of a selected construct such that the resultant construct has a sequence that is different from the original sequence; if the original sequence was a naturally-occurring sequence, the resultant sequence will be an altered (and very likely non-naturally occurring) sequence of that domain.

In addition to the fact that the specification as filed provides consistent support for the Applicant's interpretation of the meaning of "naturally-occurring" and "non-naturally-occurring", the Applicants have been consistent in explicitly articulating this interpretation throughout the prosecution history of this application.

Further, the Applicant's interpretation is consistent with the use of the phrase in the art. Essentially every construct and sequence reported in the scientific and patent literature has been made or isolated in a "non-natural" way. Both native and human-designed sequences are made and sequenced using the same types of laboratory processes. If one were to define "non-naturally-occurring" as having been made by humans, e.g., in a lab (irrespective of whether the construct had a native vs. a human-designed sequence), the phrase would be ineffective for distinguishing any construct (native or designed) from any other construct, since essentially all isolated constructs are made in a "non-natural" manner in some type of laboratory. Thus, if one of skill in the art is to accord the phrase "non-naturally-occurring" any meaning that can serve to distinguish one construct from another, the meaning must be that non-naturally-occurring monomer domain variants refer to domain variants consisting of sequences which are not found in native "naturally-occurring" monomer domains.

Finally, it should be noted that the claims do not use the terms "wild-type" and "mutant" because such usage could lead to confusion – a naturally-occurring sequence could be a wild-type sequence or a naturally-occurring mutant sequence; however, so long as such sequence is found in nature, it is considered to be naturally-occurring. Conversely, an altered or mutated sequence that is not found in nature is considered to be non-naturally-occurring.

Notwithstanding the foregoing, in an effort to expedite prosecution, the Applicants have amended the relevant claims to articulate the concept underlying the "non-naturally occurring" sequence limitation in a manner that avoids the phrase "non-naturally-occurring".

In view of the foregoing, the Applicants maintain that the claim language is clear both on its face and in view of the specification, and respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

V. Rejections under 35 U.S.C. § 102

The Examiner rejected claims 95, 100, 103, 106 and 107 under 35 U.S.C. §102(b) as anticipated by Esser, *et al.* (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988).

A. *The Present Invention*

Claim 95 is the only independent claim in the set of currently-pending claims in the present application. All other pending claims are dependent either on claim 95 or another dependent claim. Accordingly, the discussion below focuses on claim 95.

> 95. A method for producing a polypeptide, said method comprising,
> expressing a nucleic acid encoding a polypeptide, thereby recombinantly expressing the polypeptide;
> wherein the polypeptide comprises a first LDL-receptor class A monomer domain variant and a second LDL-receptor class A monomer domain variant,
> wherein each of the first and second LDL-receptor class A monomer domain variants consists of an amino acid sequence that is not present in any naturally-occurring A monomer domain,
> wherein the first and second LDL-receptor class A monomer domain variants each have a binding specificity for a target molecule,
> wherein the two domain variants are linked by a heterologous linker, and
> wherein each of first and second the LDL-receptor class A monomer domain variants comprise the following sequence:
> $C\text{-}X_{(3\text{-}15)}\text{-}C\text{-}X_{(4\text{-}15)}\text{-}C\text{-}X_{(6\text{-}7)}\text{-}C\text{-}[N,D]\text{-}X_{(3)}\text{-}[D,E,N,Q,H,S,T]\text{-}C\text{-}X_{(4\text{-}6)}\text{-}D\text{-}E\text{-}X_{(2\text{-}8)}\text{-}C$ (SEQ ID NO:331).

B. *Esser, et al.*

Esser, *et al.*, teach a mutational analysis of the ligand binding domain of the low density lipoprotein (LDL) receptor. According to Esser, *et al.*, the ligand binding domain of the LDL receptor contains seven imperfect repeats of a 40-amino acid cysteine-rich sequence (referred to by Esser, *et al.*, as Repeats 1-7). To dissect the contribution of these different cysteine-rich repeats to ligand binding, Esser, *et al.*, used oligonucleotide-directed mutagenesis to generate nine substitution mutations (each as a separate construct) in the ligand binding domain. The changes relative to the native sequence for each of the nine mutant constructs are illustrated in Fig. 1 of Esser, *et al.* Three of the constructs have mutations in Repeat 1, five constructs have mutations in Repeat 5, and one construct has a mutation in Repeat 6. None of the mutant constructs have mutations in more than one Repeat.

C. *Analysis*

For anticipation under 35 U.S.C. §102, a single reference must teach every aspect

of the claimed invention. The method of producing polypeptides encompassed by the claimed invention requires that each produced polypeptide have at least *two (a first and second) LDL-receptor class A monomer domain variants, wherein each of the first and second LDL-receptor class A monomer domain variants consists of an amino acid sequence that is not present in any naturally-occurring A monomer domain*, and wherein (*inter alia*) the two domain variants are linked by a heterologous linker. As described above, Esser, *et al.*, teach in relevant part nine substitution mutations in the ligand binding domain, resulting in sequences that are presumably not present in any naturally-occurring A monomer domain. Each of these nine substitution mutations occurs in a single Repeat: three occur in Repeat 1, five occur in Repeat 5, and one occurs in Repeat 6. None of the nine mutant constructs in Esser, *et al.*, have mutations in more than one Repeat. Put another way, none of these nine "non-naturally-occurring" constructs have mutations in more than one Repeat (where one Repeat is analogous to one LDL-receptor class A monomer domain variant). Since only one Repeat (LDL-receptor class A monomer domain variant) in each of these constructs consists of an amino acid sequence that is not present in any naturally-occurring A monomer domain, and the claimed invention requires each produced polypeptide to have at least two LDL-receptor class A monomer domains, each of which must consist of an amino acid sequence that is not present in any naturally-occurring A monomer domain, the Applicants respectfully submit that Esser, *et al.*, do not anticipate the pending claims.

In view of the foregoing, the Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

VI. Rejections under 35 U.S.C. § 103

The Examiner rejected claims 95-98, 100, 101, 103, 106 and 107 under 35 U.S.C. §103(a) as unpatentable over Esser, *et al.* (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988), in view of Bajari, *et al.*, (Biological Chemistry. Vol. 379: 10153-10162; 1998), and "if necessary", further in view of Russell, *et al.*, (Journal of Biological Chemistry. Vol. 264: 21682-21688; 1989), and Rudolph, *et al.* (The FASEB Journal. Vol. 10: p. 49-56; 1996).

A. *The Present Invention*

See above.

B. *Esser, et al.*

See above.

C. *Bajari, et al.*

Bajari, *et al.*, define the minimal binding domain of the multifunctional chicken oocyte receptor for yolk deposition (termed LR8), a relative of the low density lipoprotein receptor (LDLR). Bajari, *et al.*, used phage display of fragments derived from the entire LR8 receptor molecule and panning on the ligand -- receptor associated protein (RAP) -- to define an 80 residue stretch LR8 minireceptor. The 80 residue stretch contains 12 cysteines, and represents parts of the second, the entire third, and parts of the fourth, of the eight clustered 'ligand binding repeats' in LR8. Bajari, *et al.*, state that in addition to its use in defining minimal binding domains, the phage display approach provides powerful tools for dissection, and consequently, manipulation, of the function of receptors so as to direct their binding activity toward ligands of diagnostic and/or therapeutic interest. The reference also teaches that the phage display method is adaptable to rapid analysis of in vitro mutagenized receptor fragments in order to obtain soluble minireceptors that may interact with a defined subset of ligands, and states that LR8 is an ideal substrate to perform such studies due to its being the smallest known member of the LDLR family that can bind all of the ligands of the family identified so far.

Bajari, *et al.*, do not teach any constructs or polypeptides comprising two or more LDL-receptor class A monomer domain variants, where the two domain variants are linked by a heterologous linker and each of the variants consists of an amino acid sequence that is not present in any naturally-occurring A monomer domain.

D. *Russell, et al.*

Russell, *et al.*, assess the contribution of each of seven imperfect repeats of a 40-amino acid cysteine-rich sequence in the ligand binding domain of the low density lipoprotein (LDL) receptor via a series of site-directed mutations made <u>individually in each repeat</u>: 1)

deletion of the repeat, 2) substitution of a conserved isoleucine with aspartic acid, and 3) substitution of a conserved aspartic acid with tyrosine. Each of the mutant constructs containing substitution mutations had a mutation in only a single repeat. None of the mutant constructs contained mutations in two or more repeats simultaneously.

E. *Rudolph, et al.*

Rudolph, *et al.*, teach that insoluble, inactive inclusion bodies (formed upon recombinant protein production in transformed microorganisms) can be isolated by solid/liquid separation. The reference discloses folding procedures for efficient in vitro reconstitution of complex hydrophobic, multidomain, oligomeric, or highly disulfide-bonded proteins. Rudolph, *et al.*, further note that modification of the protein sequence has been exploited to improve in vitro folding.

Rudolph, *et al.*, teach nothing about the LDL receptor or A-domains, indeed, Rudolph, *et al.*, teach nothing about any repeated domains having cysteine-rich sequences.

F. *Analysis*

As noted above, Esser, *et al.*, do not teach polypeptides comprising at least two LDL-receptor class A monomer domain variants, wherein each of the two variants consists of an amino acid sequence that is not present in any naturally-occurring A monomer domain, and wherein (*inter alia*) the two domain variants are linked by a heterologous linker. This failing is not remedied by any of the secondary references cited by the Examiner. Neither Esser, *et al.*, nor any of Bajari, et al., Russell, et al., or Rudolph, et al., provide any motivation or suggestion (explicit or implicit) to arrive at the methods of the present invention.

As stated in the abstract of Esser, *et al.*, the studies performed therein were done "*[t]o dissect the contribution of these different cysteine-rich repeats to ligand binding*" by the human (native) LDL receptor (emphasis added). As detailed above, Esser, *et al.*, teach nine substitution mutations in the ligand binding domain, where each of the nine mutations occurs in a single Repeat; none of the nine mutant constructs taught by Esser, et al., have mutations in more than one Repeat.

Similarly, Russell, *et al.*, teach in relevant part seven substitution mutations where aspartic acid is substituted for a conserved isoleucine in each of the seven repeats. As in Esser, *et al.*, each of these mutant constructs contains only a single mutation – the first has the mutation in the first repeat, the second has it in the second repeat, and so on for all seven repeats. Russell, *et al.*, further teach another set of mutant constructs where a conserved Asp between the 5^{th} and 6^{th} cysteines is mutated, again on a repeat-by-repeat basis, to a Tyr. As above, none of the mutant constructs containing the Asp-to-Tyr mutation has the mutation in two or more repeats simultaneously. Furthermore, the Asp mutated by Russell, *et al.*, is required by the SEQ ID NO:331 sequence limitation of the claimed invention; the constructs containing the Asp-to-Tyr mutation fall outside of this sequence limitation.

Generating mutant constructs with point mutations in one or another of the Repeats, as done by Esser, *et al.*, and Russell, *et al.*, is presumably a scientifically-preferred method for determining the contributions to ligand binding of the different repeats. If either Esser, *et al.*, or Russell, *et al.*, had generated constructs having multiple mutations simultaneously in different repeats, the results would likely have been considerably more difficult to interpret (*e.g.*, did altered binding result from mutations in Repeat *x* or from mutations in Repeat *y*?). Taken together, the collective guidance from both references thus seems to be that if any subsequent researchers wish to further dissect contributions of the sequences of different cysteine-rich repeats to ligand binding in the native LDL receptor (or indeed, in any naturally-occurring protein containing LDL-receptor class A monomer domains), such researchers should make mutations in one repeat at a time, and not multiple repeats simultaneously as is required by the methods of the present invention.

Bajari, *et al.*, teach a different approach from that of Esser, *et al.*, or Russell, *et al.*, to the analysis of the ligand binding regions of A-domain-containing receptors – rather than making individual point mutations in the ligand binding domain (or deleting specified regions thereof), Bajari, *et al.*, randomly generate fragments of the entire receptor protein and use phage display to identify those fragments that have ligand binding activity. The constructs taught by Bajari, *et al.*, thus presumably do <u>not</u> contain LDL-receptor class A monomer domain variants

consists of amino acid sequences that are not present in any naturally-occurring A monomer domain, although they do contain fragments of LDL-receptor class A monomer domain variants having *naturally*-occurring amino acid sequences. However, such fragments do not satisfy the sequence requirements of SEQ ID NO: 331 because SEQ ID NO: 331 defines a complete LDL-receptor class A monomer domain, and not a fragment thereof.

As indicated above, Bajari, *et al.*, teach that the phage display method is adaptable to rapid analysis of in vitro mutagenized receptor fragments in order to obtain soluble minireceptors that may interact with a defined subset of ligands, and states that LR8 is an ideal substrate to perform such studies due to its being the smallest known member of the LDLR family that can bind all of the ligands of the family identified so far. The Applicants note that this teaching is directed to the analysis of mutagenized receptor fragments of *a particular selected member* of the LDLR family ("...LR8 is an ideal substrate to perform such studies..."). Nothing in Bajari, *et al.*, can fairly be said to suggest the making of the polypeptides as claimed by the present invention, where such polypeptides are generated based not on any particular member of the LDLR family, but rather on a consensus sequence provided by the Applicants.

The reference of Rudolph, *et al.*, teaches nothing about any repeated domains having cysteine-rich sequences (the LDL receptor, A-domains or otherwise), and is therefore not address any further in this paper.

Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *In re Kahn*, 441 F.3d 988 (Fed. Cir. 2006). As the Supreme Court stated in KSR International Co. v. Teleflex Inc. et al., "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." In the present case, the Examiner has picked out various aspects of the claimed invention and stated how selected teachings from each reference could allegedly be combined to arrive at the claimed invention. However, the Examiner has not articulated any reasoning or rationale *why* one of skill in the art would combine the disparate teachings of Bajari,

et al., Russell, *et al.*, or Rudolph, *et al.*, with Esser, *et al.*, along the lines of the invention to arrive at the claimed invention.

In view of the foregoing, the Applicants respectfully request withdrawal of the rejection(s) under 35 U.S.C. §103.

VII. Double Patenting

The Examiner provisionally rejected claim 95-98 and 103 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21, 22, 24, 25 and 31 of copending Application No. 10/971,679, filed 10/22/2004.

The present application was filed on 10/24/2003. Where a provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application may be rejectable on other grounds, the MPEP (§804) instructs the Examiner to withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. Accordingly, the Applicants respectfully request the Examiner to withdraw this provisional nonstatutory obviousness-type double patenting rejection and allow this application to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 650-244-3147.

The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Deposit Account No. 01-0519 in the name of Amgen Inc.

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